International Journal of Advance and Applied Research
www.ijaar.co.in
ISSN – 2347-7075 Impact Factor – 7.328
Peer Reviewed Bi-Monthly
Vol. 11 No. 4 March-April 2024

Solid Dispersion by Melt Method to Improve Solubility and Oral Bioavailability of Ritonavir

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DOI- 10.5281/zenodo.11124407

Abstract:
Ritonavir, a potent antiretroviral drug, suffers from poor water solubility, leading to challenges to improve bioavailability and therapeutic efficacy. In this study, we aimed to enhance the solubility of ritonavir through the solid dispersion melt method and subsequently formulate it into tablets for improved oral delivery. Solid dispersion melt method was employed to prepare ritonavir solid dispersions using various carriers, including polymers such as, Poloxamer 407, poloxamer 188, PVP K 30, and different evaluation are performed such as Fourier-transform infrared spectroscopy (FTIR), XRD, *In-vitro* release study. solubility of ritonavir and prepared solid dispersion formulations are evaluated and show significant enhancements of solubility compared to the pure drug, physicochemical properties, and compatibility studies are evaluated. ritonavir solid dispersion formulation(s) were incorporated into tablet formulations using suitable excipients to ensure stability, and suitable dissolution characteristics. The tablets were evaluated for various pharmaceutical parameters such as hardness, friability, disintegration time, and dissolution profile. From the formulated batches DS1 to DS6, The DS1 show the highest percentage release up to 95.2%, and all other parameters of tablet are passes.

Keywords: Solubility; Solid Dispersion (SDP); melting method; Bioavailability.

Introduction:

Due to its simplicity and ease of consumption, the oral route of drug administration is the most popular and favored way of delivery; nonetheless, it might provide challenges if the medication has poor membrane penetrability or is poorly soluble in water [1]. Insufficient bioavailability is frequently caused by poorly water-soluble medicines' weak solubility and slow rate of dissolution in aqueous gastrointestinal fluids. Lipophilic molecules present significant delivery challenges, such as incomplete release from the dosage form, insufficient bioavailability, increased food effect, and high inter-patient variability. This is especially true of molecules classified as class II as well as IV in the biopharmaceutics classification system (BCS), which dissolve slowly, poorly, and irregularly [2].

The process of dispersing one or more active substances in an inert carrier or matrix in a solid form using a melting (fusion), solvent, or melting solvent method is known as solid dispersion technology. Solid goods are often made up of a hydrophilic matrix and a hydrophobic medication, or at least two distinct components. The matrix could be amorphous or solid. The medication may be distributed as crystalline, amorphous, or molecular particles (clusters) [3].

Particle size is decreased in solid dispersions, and the medicine is molecularly disseminated in the dissolving solvent following carrier dissolution. This idea is applied to medication release using solid dispersions, which combine highly soluble carriers with low water soluble drugs. It forms a high surface area, which enhances the bioavailability and increases the rate of dissolution.[4] Ritonavir is a drug that is mostly used to treat Viral/AIDS by preventing the HIV protease enzymes from functioning, which is necessary for the virus to replicate. In 1996, ritonavir—which was initially created by Abbott Laboratories—was granted approval for use in medicine within the US. It is a member of the class of medications known as protease inhibitors, which function by obstructing the protease enzyme, which stops the virus from proliferating and lowers the body's viral load.[5]

Material:

Ritonavir was obtained gift sample from lupin Aurangabad Maharashtra. Poloxamer 407, poloxamer 188 and PVP K 30 is obtained from SK Enterprise Pune.

Method:

This process involves heating the physical mixture containing the water-soluble carrier until it melts, at which point the medication is added. After that, the melted fluid is quickly cooled and hardened while being vigorously stirred in an ice bath. After the final solid mass has been ground, pulverized, and sieved, tableting agents can be used to compress

it into tablets. The makeup of a binary system, or the choice of carrier and the proportion of drug weight in the system, determines its melting point.[6]

Formulation table

Table no 1: Formulation Table

Batch number	Ingredient		Ratio of polymer	
	Drug (mg) Ritonavir	Polymer		
SD1	100	Poloxamer 407	50	-
SD2	100	Poloxamer 407	-	100
SD3	100	Poloxamer 188	50	-
SD4	100	Poloxamer 188	-	100
SD5	100	PVP K 30	50	-
SD6	100	PVP K 30	-	100

Direct compression method:

The process of direct compression was employed to create the tablets of 200 mg tablet was punched out using a single-punch tablet compression equipment (Karnavati). Solid dispersion was taken in a ratio (1: 0.5) and remaining lactose, Magnesium Stearate was used to make punch 200 mg weight of tablets.[7]

Table No 2: Formulation of Tablet Containing Solid Dispersion of Ritonavir

Sr. no	Ingredient	Quantity (mg)
1	Ritonavir Solid dispersion	150
2	Lactose	45
3	Magnesium Stearate	5

Characterization Of Prepared Ritonavir Solid Dispersion:

1. Study of Solubility2. Infrared spectroscopy Fourier transform (FT-IR) 3. X-ray powder diffraction (PXRD)
4. Pre-Compression Evaluation Parameters of powder
5. Post-Compression Evaluation Parameters of tablets
6. *In-vitro* drug release

1. Solubility

The solubility of ritonavir and formulation batches was carried out by taking amount of 10 mg of pure drug and prepared batches were separately in to purified water, to obtained saturated solution. By using thermostatically controlled rotary shaker the sealed flasks were agitated for 24 hrs at 37°C. Then the aliquot was filter by using 0.45 µm membrane filter. Then the filtrate was diluted and analysed UV visible at wavelength 240 nm. [8]

2. Infrared spectroscopy Fourier transform (FT-IR): Physicochemical characterization was done using Fourier transform infrared (FTIR) spectra. The medication's identity and its interactions with polymers are disclosed by the FTIR spectra. An FTIR spectrum was obtained for the medication in its pure form as well as the batch of nanocrystal that underwent optimization. A nanocrystal sample was placed on a surface intended to hold samples for examination. The wave number range of 4000-400 cm1 was covered by the spectrum scan. [9]

3. Powder diffraction of X-rays (PXRD): Utilizing Cu K 2α light at a voltage level of 40 kV and an applied flow of 25 mA, a diffractometer with X-rays (a Bruker, D 8 Advanced, USA) was used to conduct the PXRD examination. The samples were scanned at 2: at 10 and 60°. [10]

4. Pre-Compression Evaluation Parameters of Powder [11]

I] Angle of Repose:

The funnel method was used to calculate the angle of repose. The 10 grams of precisely weighed granules were placed in a funnel. The funnel's height was modified so that the leading edge of the funnels just brushed the top of the granule pile. Granules were permitted to freely flow through a funnel onto a spotless surface. The cone's diameter was measured, and the angle of repose was calculated using the equation that follows.

II] Bulk density:

A graduated cylinder was filled with the individually weighed powder, and the first bulk volume was recorded. The following formula was used to compute the bulk density:

$$\text{Bulk density} = \frac{\text{weighed of powder}}{\text{bulk valum}}$$

III] Tapped Density:

The powder was put into the USP tapped density tester and tapped continuously at a rate of 200 drops per minute until the final volume difference was less than 2 percent. The tapping volume was noted for it. The following formula was utilized to determine the tapped density:

$$\text{Tapped density} = \frac{\text{weight of powder}}{\text{tapped volume}}$$

IV] Carr's Index:

It is calculated using below formula,

$$\text{Carr's index} = 100 \text{ X } \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}}$$

V] Hausner's ratio:

The Hausner's Ratio of a material is calculated with the following formula,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Post-Compression Evaluation Parameters of tablets [12]

I] Physical Appearance:

Tablets were studied for colour, shape, size and thickness.

II] Weight variation Test:

Weight variation test perform by randomly selecting 20 tablets and weigh on electronic balance and percentage weight variation is calculated.

III] Hardness Test:

For the purpose of handling shocks during manufacture, packaging, and shipping, a tablet needs to be strong enough and resistant to friability. To find out how hard the tablet was, the Monsanto Hardness Tester a simple device was used. A pill and the tester's mouth were placed vertically in between them. A screw gauge and springs are used to lock the two jaws into position. The screw was rotated to increase the load, and at collapse, the spring's applied pressure was measured in kilograms. For this test, six tablets were used.

V] Friability Test:

Tablets were tumbled in a Roche's Friabilator as part of the friability test. With each revolution of the plastic chamber, which rotates at 25 rpm and drops the tablets six inches away, the apparatus combined the effects of shock and abrasion on twenty tablets.

This was done for one hundred rotations. The following formula was used to determine the tablets' % friability after they had been degusted and weighed once more.

$$\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{ x100}$$

5. In-vitro Release Study:

In-vitro release utilizing USP type II equipment (paddle type) (Electro lab TDT-08L). The samples were put in a 900-mL 0.1N HCl container with a temperature of 37 ± 0.5°C and a paddle rotating speed of 50 rpm. At predetermined intervals, 5 ml aliquots were removed using a 0.45 µm filter needle and refilled with an identical volume of new dissolving medium. The amount of released ritonavir was measured spectrophotometrically at 240 nm, the drug's maximum absorbance (λmax), using a UV-visible spectrophotometer (Shimadzu, Japan). The percentage of cumulative ritonavir release was then plotted against the sample collection period to create the release profile.

Result and Discussions:

1. U-Visible Spectrophotometric Characterization of Ritonavir (λmax) Determination:

A precise weight of 10 mg of ritonavir was transferred to a 10 ml volumetric flask, and a volume of ethanol was added. Finally, the standard solution of ritonavir in ethanol was ready to be scanned within 200 and 400 nm on a UV visible double beam spectrophotometer (Systronics 2201) to record the wavelength maximum absorption (max). One milliliter was removed and added to the ten milliliter volumetric flask from this solution. The maximum absorption was found to be at 239.2 nm.

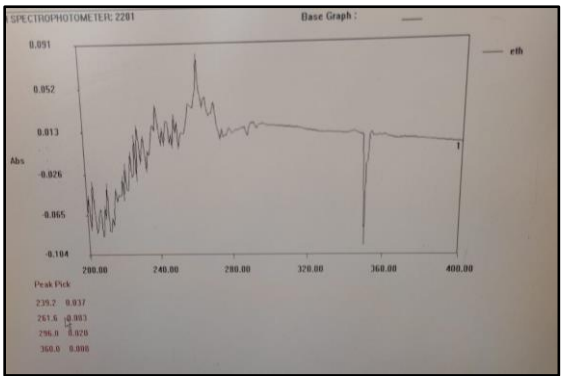

Fig .no 1: Determination of λ_{max} of Ritonavir

2. Determination of Calibration Curve of Ritonavir In 0.1N HCL:

I. Making 0.1N HCL: Using a pipet, take 2.1 ml of concentrated HCL and dilute it to 250 ml in a 250 ml volumetric flask with distilled water.

II. Stock solution preparation: A 10 ml volumetric flask was filled with precisely weighed 10 mg of ritonavir. It was dissolved with the aid of 0.1N HCl, and the volume was increased to the required level so that the stock-1 solution's concentration of ritonavir was 1000 µg/ml. Using the same solvent system, 1 ml of the stock-1 solution was further diluted to 10 ml to create the stock-2 solution (100 µg/ml).

III. Standard solution preparation: To get a final drug concentration in the range of 5–25 µg/ml, appropriate aliquots of the stock-2 solution of ritonavir (5, 10, 15, 20, and 25 µg/ml) were precisely pipetted out into 10 ml volumetric flasks and diluted up to the mark with solvent.

Table no 3: Concentration and Absorbance of Ritonavir in 0.1 N HCL

Sr. no	Concentration µg/ml	Absorbance
1	5	0.105
2	10	0.133
3	15	0.180
4	20	0.230
5	25	0.280

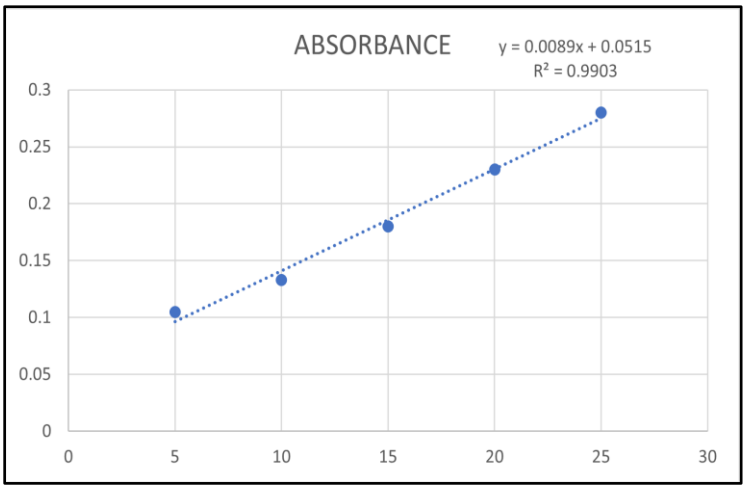

Fig. no 2: Calibration Curve of Ritonavir in 0.1 N HCL

3. Solubility Study:

The formulations of SD1, DS3, and SD4 had the maximum solubility in water (50.7, 42.74, and 42.45, respectively), in comparison to pure ritonavir (31.8). Notably, ritonavir's solubility in water has increased in other formulations as well.

Table no 4: Solubility of Pure Ritonavir and Prepared Formulation

Formulation Code	Solubility (µg/Ml)
PURE DRUG	31.8
SD1	50.7
SD2	33.1
SD3	42.74
SD4	42.45
SD5	32.08
SD6	35.2

4. Fourier Transfer Infrared Spectroscopy (FTIR) Analysis:

The expansive, vigorous range for alcohol and carbonyl group are located in the spectrum of 3600-3200 cm^{-1} and 1760-1690 cm^{-1} respectively. For pure drug i.e. ritonavir shows the -OH and C=O stretching peak at 3352.77 cm^{-1} and 1715.27 cm^{-1} respectively. For Drug and polymer combination of PVP K 30, Poloxamer 407, Poloxamer 188. For Drug and polymer combination of PVP K 30, Poloxamer 407, Poloxamer 188, individually show the peak for C=O stretching at 1715.86, 1715.53, 1715.81, 1715.26 respectively.

It was found from IR study that all the characteristics peak of ritonavir and combination of pure drug and polymers evident. Hence its conform that the pure drug and polymer does not show any interaction between each other. FTIR spectra for pure drug shown in fig.no 3.

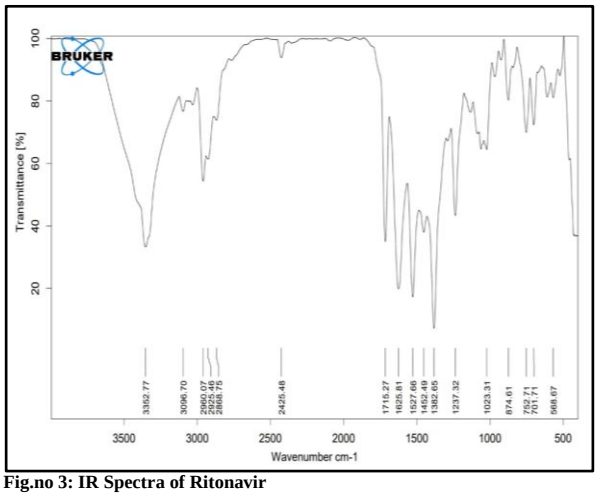

Fig.no 3: IR Spectra of Ritonavir

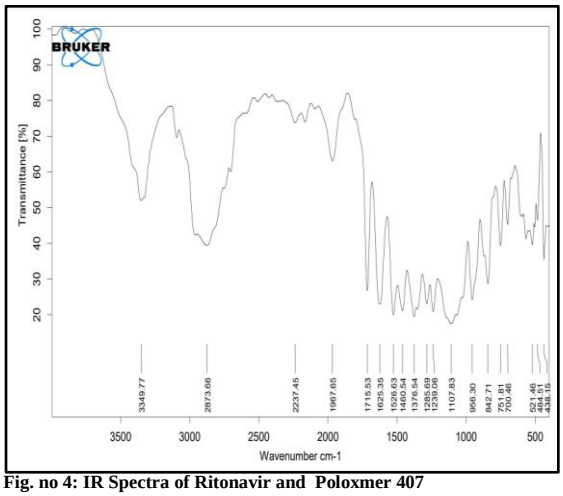

Fig. no 4: IR Spectra of Ritonavir and Poloxmer 407

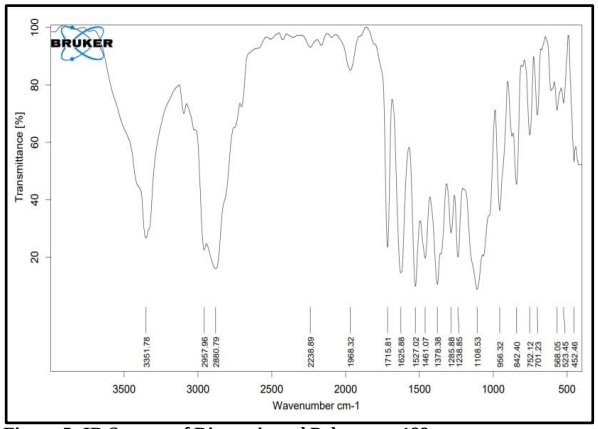

Fig. no 5: IR Spectra of Ritonavir and Poloxamer 188

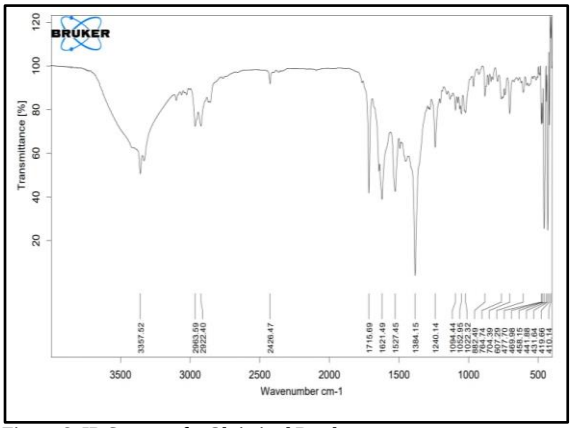

Fig. no 6: IR Spectra of Obtimized Batch

Table no 5: Interpretation of FTIR Spectra of Pure Drug, Drug and Polymer and Optimized Batch

Functional Group	Absorbance Frequency	Ritonavir	Ritonavir and PVP K30	Ritonavir and POLOXOMER407	Ritonavir and POLOXOMER188	Optimized batch
C=O STREACHING	1760-1690	1715.27	1715.86	1715.53	1715.81	1715.69
C-H STREACHING	2850-2917	2868.57	2922.25	2873.66	2880.79	2922.4
C=N	1690-1640	1625.81	1621.51	1625.35	1625.88	1621.49
-OH	3600-3200	3352.77	3357.6	3349.77	3351.78	3357.52
R-S-H	~2550	2425.48	2426.44	2237.45	2238.89	2426.47
C=C STREACHING	1600-1475	1527.66	1527.05	1526.63	1527.02	1527.45

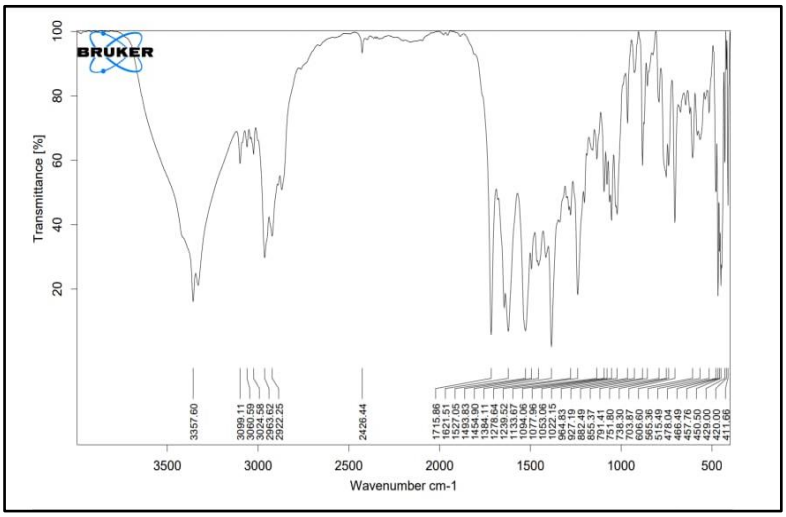

Fig. no 7: IR Spectra of Ritonavir and PVP K 30

5. Powder X-Ray Diffraction (PXRD):A compound powder's nature was ascertained by X-ray diffraction examination. The ritonavir solid dispersion of SD1 batch's powder XRD diffractogram has distinctive crystalline peaks at 26.751, 13.14, 10.644, and 4.126, as shown in figure no 8.

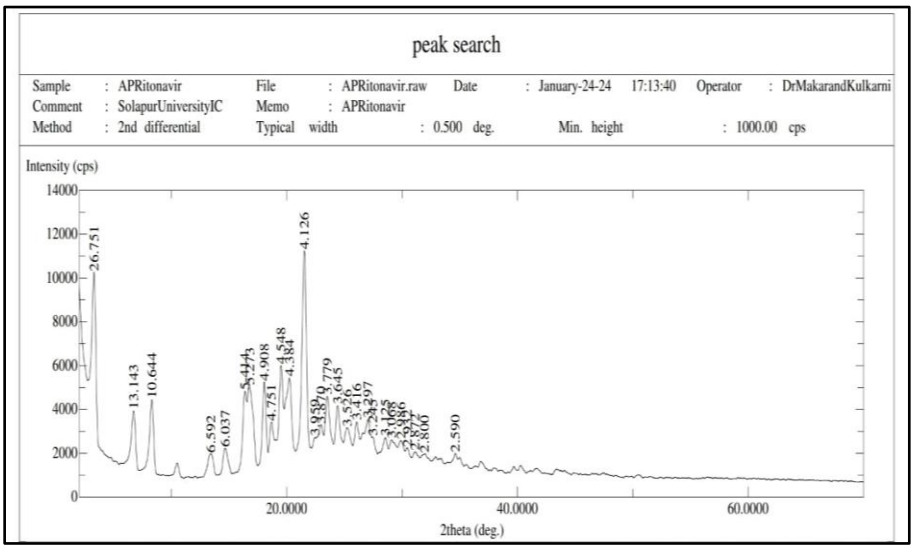

Fig. no 8: X-Ray Diffraction of Optimized Batch

6. Precompression Evaluation of powder

The precompression parameters of the ritonavir nanocrystal for several parameters, including bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio was show in table no 6.

Table no: 6 Precompression Evaluation of powder

Formulation code	Bulk density ($g/cm^{3)}$	Tap density ($g/cm^{3)}$	Angle of Repose	Carr's index (%)	Hausner's ratio
SD1	0.050	0.13	24	40	1.69
SD2	0.053	0.2	28	38	1.65
SD3	0.058	0.1	25.5	42	1.72
SD4	0.048	0.19	29	45	1.63
SD5	0.051	0.15	28.7	39	1.68
SD6	0.046	0.09	26	48	1.75

Post Compression Evaluation of Solid Dispersion of Ritonavir Tablet

The post-compression parameter of ritonavir nanocrystal tablet like thickness, hardness, friability, weight variation, show in table no 7.

Table no: 7 Post Compression Evaluation of Tablet

Formulation code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (% Deviation)
SD1	3.3	5	0.82	199.5±2.3
SD2	3.2	5	0.79	200.2±2.23
SD3	3	5	0.73	199.25±2.67
SD4	3.51	4	0.83	198.55±1.93
SD5	3.2	5	0.92	200.35±1.92
SD6	3.2	6	0.86	199.65±2.13

8. *In-vitro* Release Studies:

The *In-vitro* release studies were investigations for all batches from SD1 to SD6 from 15 to 150 minutes, and the DS1 batch exhibits good release 98.95% and was selected as an optimized batch.

Tablet no: 8 *In-vitro* release study of solid dispersion of ritonavir

Time	SD 1	SD 2	SD3	SD4	SD5	SD6
15	8.8	9.2	12.27	8.73	5.8	8.9
30	25.2	22.4	29.2	12.38	15.6	26.4
45	43.5	43.5	45.53	33.20	28.5	39.1
60	55.6	52.2	60.5	38.40	42.5	52.4
90	61.7	62.8	71.8	42.22	50.6	63.8
120	82.3	70.2	79.9	58.62	63.8	72.1
150	95.2	82.8	89.2	72.05	80.2	92.5

Conclusion:

Solid Dispersion of ritonavir has proven to be an effective strategy for enhancing its solubility, dissolution rate resulting in improved oral bioavailability. The physical compatibility FTIR studies proved that there was no interaction between the drug and polymers. The solid dispersion of ritonavir were prepared by melting method by using polymers such as Poloxamer 407, poloxamer 188, and PVP K30, in different ratio. Total 6 batches of solid dispersion were prepared. The Preformulation study of powder was performed which shows results with passable range. After that post formulation evaluation of the tablet was prepared and evaluated for different quality control parameters, which reflects the results at optimum level. The percentage drug release from formulation SD1, SD3 and SD5 was found to be 95.2%, 89.2%, and 92.5% respectively. Among of six batches SD1 shows highest dissolution (95.2 %) and SD 3 is selected as optimized batch according to dissolution and particle size. P-XRD graphs of batch SD 3 show their crystalline nature. From this research work it was concluded that the solid dispersion of ritonavir produced by melting method using Poloxamer 407, poloxamer 188 and PVP K-30,as polymers showed increase in solubility of ritonavir.

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